UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
MAHATAN, CHANNING

ART UNIT	PAPER NUMBER
1631	8

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

-- *The MAILING DATE of this communication appears on the cover sheet with th correspond nce address --*

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE <u>3</u> MONTH(S) FROM
THE MAILING DATE OF THIS COMMUNICATION.
- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed
  after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any
  earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *25 March 2003* .

2a) ☐ This action is **FINAL.**   2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is
closed in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) ___ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-15* is/are rejected.

7) ☒ Claim(s) *14* is/are objected to.

8) ☒ Claim(s) *1-15* are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some * c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____ .

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage
application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application (PTO-152)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2 Sheets* .	6) ☐ Other: .

DETAILED ACTION

APPLICANTS' ELECTION

Applicants' election with traverse of Group I (claims 1-10 and 15; drawn to a method of

modeling a directed evolution protocol and system) in Paper No. 7, filed 25 March 2003, is

acknowledged. The traversal argument, in view, of amendments to claims 11-14 (Groups II and

III; directed to of method claims and no longer directed to product claims) in Paper No. 7, filed

25 March 2003, is found persuasive. Therefore, claims 1-15 drawn to methods of modeling a

directed evolution protocol and system are under examination.

CLAIMS UNDER EXAMINATION

Claims herein under examination are claims 1-15.

Claims Rejected Under 35 U.S.C. § 101

35 U.S.C. § 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of
> matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the
> conditions and requirements of this title.

Claims 1-14 are rejected under 35 U.S.C. § 101 because the claimed invention is directed

to non-statutory subject matter.

NON-STATUTORY SUBJECT MATTER

Claims 1-14 are rejected under 35 U.S.C. § 101 because the claimed invention is directed

to non-statutory subject matter. The claimed invention is directed to a "method of modeling a

directed evolution protocol"/"method of providing an isolated nucleic acid molecule".

M.P.E.P. section entitled "Nonstatutory Subject Matter" (pages 2100-12, Columns 1-2)
states:

> Claims to processes that do nothing more than solve mathematical problems or manipulate
> abstract ideas or concepts are more complex to analyze and are addressed below.

If the "acts" of a claimed process manipulate only numbers, abstract concepts or ideas, or signals representing any of the foregoing, the acts are not being applied to appropriate subject matter. Schrader, 22 F.3d at 294-95, 30 U.S.P.Q.2d at 1458-59. Thus, a process consisting solely of mathematical operations, i.e., converting one set of numbers into another set of numbers, does not manipulate appropriate subject matter and thus cannot constitute a statutory process.

Further, M.P.E.P. section entitled "Statutory Process Claims" (page 2100-15, Column 1-2) states:

A claim that requires one or more acts to be performed defines a process. However, not all processes are statutory under 35 U.S.C. 101. Schrader, 22 F.3d at 296, 30 U.S.P.Q.2d at 1460. To be statutory, a claimed computer-related process must either: (A) result in a physical transformation outside the computer for which a practical application in the technological arts is either disclosed in the specification or would have been known to a skilled artisan (discussed in i) below), or (B) be limited to a practical application within the technological arts (discussed in ii) below). See Diamond v. Diehr, 450 U.S. at 183-84, 209 U.S.P.Q. at 6 (quoting Cochrane v. Deener, 94 U.S. 780, 787-88 (1877)) ("A [statutory] process is a mode of treatment of certain materials to produce a given result. It is an act, or a series of acts, performed upon the subject-matter to be transformed and reduced to a different state or thing.... The process requires that certain things should be done with certain substances, and in a certain order; but the tools to be used in doing this may be of secondary consequence."). See also Alappat, 33 F.3d at 1543, 31 U.S.P.Q.2d at 1556-57 (quoting Diamond v. Diehr, 450 U.S. at 192, 209 U.S.P.Q. at 10). See also id. at 1569, 31 U.S.P.Q.2d at 1578-79 (Newman, J., concurring) ("unpatentability of the principle does not defeat patentability of its practical applications") (citing O 'Reilly v. Morse, 56 U.S. (15 How.) at 114-19). If a physical transformation occurs outside the computer, a disclosure that permits a skilled artisan to practice the claimed invention, i.e., to put it to a practical use, is sufficient. On the other hand, it is necessary for the claimed invention taken as a whole to produce a practical application if there is only a transformation of signals or data inside a computer or if a process merely manipulates concepts or converts one set of numbers into another.

The computation steps/processes of claims 1-14 are merely "mental" processes of performing mathematical operations (manipulation of numbers) applied to a computer. The claims do not recite any concrete or tangible results; therefore the claims do not recite statutory subject matter.

Claims Rejected Under 35 U.S.C. § 112 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Factors to be considered in determining whether a disclosure would require undue

experimentation have been summarized in Ex parte Forman, 230 U.S.P.Q. 546 (B.P.A.I. 1986)

and reiterated by the Court of Appeals in In re Wands, 8 U.S.P.Q. 2d 1400 at 1404 (C.A.F.C.

1988). The factors to be considered in determining whether undue experimentation is required

include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3)

the presence or absence of working examples, (4) the nature of the invention, (5) the state of the

prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the

art, and (8) the breadth of the claims. The Board also stated that although the level of skill in

molecular biology is high, the results of experiments in genetic engineering are unpredictable.

While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed

below.

SCOPE OF ENABLEMENT

Claims 1-15 are rejected under 35 U.S.C. § 112, first paragraph, because the

specification, while being enabling for the disclosed method of "modeling framework for

predicting the number, type, and distribution of crossovers in directed evolution experiments"

such that the "framework provides for determining how fragmentation length, annealing

temperature, sequence identity, and number of shuffled parent sequences affect the number, type,

and distribution of crossovers along the length of reassembled sequences" (page 3, lines 23-27;

and pages 5-15), does not reasonably provide enablement for the "method of modeling a directed

evolution protocol" by any other means. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to use the invention

commensurate in scope with these claims. For instance, claims 1 (lines 2-3) and 15 (line 3-4)

recites the step of "applying equilibrium thermodynamics", however, the specification provides

for limited guidance as to how to apply said equilibrium thermodynamics. The specification

states, "annealing events during reassembly are modeled as a network of reactions, and

equilibrium thermodynamics is used to quantify their conversions and selectivities.... The

thermodynamics of duplex formation is analyzed by using nearest-neighbor parameters that

describe the enthalpic and entropic contributions of specific nucleotide pairs in the overlapping

region" and provides for a limited framework of algorithms to calculate "equilibrium

thermodynamics" (pages 3-4, lines 30-32 and 1-9, respectively; page 6, lines 17-25; and the table

on pages 7 & 8). Further, the specification indicates that the reassembly algorithm/procedure is

modeled as a successive sequence of annealing events used to postulate a set of relations

probability that a full-length reassembled sequence has crossovers, wherein algorithms for the

calculation of said probabilities is indicated (pages 12-14; and Figure 2). It is disclosed that

utilization of the algorithm framework allows quantification of the statistics of any type of

crossover (page 14, lines 21-24). Thus, the specification fails to provide for other means (i.e.

modeling of annealing events and reassembly algorithm) of "modeling a directed evolution

protocol". No other methods of "modeling a directed evolution protocol" are disclosed. None

appear to have been known in the art. No guidance, direction, or examples are provided such

that one of ordinary skill in the art would have known practice to use the claimed invention.

Additionally, claim 10 is not commensurate in scope with the specification with regard to

the instantly claimed step where the "assembly algorithm excludes silent crossovers". The

specification indicates "if the annealing of a fragment m to a growing template ending with a

fragment from parent k is equivalent to the continuation of the template with the nucleotides

from parent *k*, no crossover is counted" (page 13, lines 13-22; and page 17, lines 13-16).   No

other methods are taught for excluding silent crossovers are disclosed and the specification

provides no guidance as to other methods for excluding silent crossovers. None appear to have

been known in the art. No guidance, direction, or examples are provided such that one of

ordinary skill in the art would have known practice to use the claimed invention.

Claims Rejected Under 35 U.S.C. § 112 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for

failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention.

VAGUE AND INDEFINITE

Claims 1, 15, and all claims dependent therefrom are indefinite due to the lack of clarity

of the claim language failing to recite a final process step, which agrees back with the preamble.

The preamble states that it is a "A method of modeling a directed evolution protocol" (claim

1)/"A system of modeling a directed evolution protocol" (claim 15), however the claim recites a

final step "parameterizing an assembly algorithm using statistics of hybridization" (claim 1), "an

article of software for determining statistics of hybridization of the plurality of sequences to

parameterize an assembly algorithm by applying equilibrium thermodynamics to the plurality of

sequences" (claim 15). There is no indication of a "modeling" step or as recited in the preamble.

While minor details are not required in method/process claims, at least the basic step must be

recited in a positive, active fashion. Clarification of the metes and bounds of the claim is

requested, via clearer claim wording.

Claims 12 and 13 recite "wherein a vector" or "wherein a host cell", respectively, which

is confusing. It is unclear as to the limitations dependent claims 12 and 13 provide for because

said claims are directed to a physical limitation (i.e. vector and host cell). In contrast, claim 11 is

interpreted to be directed to a computational/*in silico* method where the nucleotide sequence is a

character string rather than an actual piece of DNA (Refer to Rejection Under 35 U.S.C. § 101).

Clarification of the metes and bounds, via clearer claim language, is requested.

Claims Rejected Under 35 U.S.C. § 102

(a) the invention was known or used by others in this country, or patented or described in a printed
publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public
use or on sale in this country, more than one year prior to the date of application for patent in the United
States.

Claims 1-15 are rejected under 35 U.S.C. § 102 (a) as being anticipated by Moore et al.

Moore et al. discusses predictive models (computationally) for quantifying the outcome

of DNA recombination in directed evolution experiments for the generation of enzymes, thereby

allowing for (i) tracking DNA fragment size distribution after random fragmentation and

subsequent assembly into genes of full length and (ii) estimating the fraction of the assembled

full length sequences matching a given nucleotide target (Abstract). Figure 1 illustrates the DNA

shuffling wherein a first initial set of parent DNA sequences undergo random fragmentation and

are then reassembled (page 2, columns 1-2, lines 1-36 and 1-8, respectively). The authors

indicate reasons for the development of (optimize mix and setup of initial sequence libraries and

the effect of parameters; i.e. fragment length, annealing temperature, and shuffling cycles) and

describe predictive models (i.e. random fragmentation model, fragment assembly model, and

sequence matching model (pages 2-5, beginning on column 2, line 9). Further, the authors state

the sequence matching model takes into account both crossovers (silent crossovers) and linkage

(page 4, column 2, lines 1-19). It is noted that the presented modeling and optimization

framework is currently being extended to combine DNA shuffling with incremental truncation

libraries (page 7, column 1, lines 5-11). Thus, fairly disclosing the limitations to SCRATCHY

(Refer to below notation of SCRATCHY in the specification). Therefore, Moore et al.

anticipates the claimed invention.

Claims 1-15 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Ostermeier et

al.

Ostermeier et al. describe a methodology of incremental truncation for the creation of

hybrid enzymes (ITCHY) that creates combinatorial libraries between genes independent of

DNA homology (Abstract; and page 1205, column 1, lines 19-34). The authors describe and

illustrate the combinatorial protein-engineering model of ITCHY (page 1205-1206, beginning on

column 2, line 9; and Figure 1). Ostermeier et al. compare ITCHY and DNA shuffling to create

interspecies fusion libraries (page 1206, beginning on column 1, line 38; and Figure 3). Further,

the authors state that "ITCHY libraries create all possible crossovers between two genes" and

"DNA shuffling of ITCHY libraries allows one to create a library of genes with multiple

crossovers that include crossovers at regions of no homology" (page 1208, column 2, lines 50-

58). Thus, Ostermeier et al. anticipates the claimed invention.

It is noted that the specification indicates "SCRATCHY can be abstracted as the family

DNA shuffling of an artificially created superfamily containing all single crossover hybrids

between two genes of interest" (page 21, lines 24-32).

OBJECTION TO CLAIM

Claim 14 is objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 14 (lines 1-2) recites the phrase "the nucleotide sequence encodes a protein" which fails to further limit the claim from which it depends from (claim 11, line 3 "a nucleotide sequence having an amino acid sequence". Applicants are required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

OBJECTION TO DISCLOSURE

The disclosure is objected to because of the following informality:

The disclosure on page 17, line 6 contains a typographical/grammatical error: "...invention. only after...", wherein the word "only" requires capitalization.

Appropriate Correction Is Requested.

No Claims Are Allowed.

EXAMINER INFORMATION

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 C.F.R. § 1.6(d)). The CM1 Fax Center number is either (703) 308-4242 or (703) 305-3014.

Any inquiry concerning this communication or earlier communications from the
examiner should be directed to Channing S. Mahatan whose telephone number is (703) 308-
2380. The examiner can normally be reached on M-F (8:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's
supervisor, Michael P. Woodward, Ph.D., can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be
directed to Legal Instruments Examiner, Tina M. Plunkett, whose telephone number is (703)
305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

Date: May 30, 2003

Examiner Initials: CSM

MARIANNE P. ALLEN
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